EPINASTINE HYDROCHLORIDE- epinastine hydrochloride solution/ drops
Breckenridge Pharmaceutical, Inc.

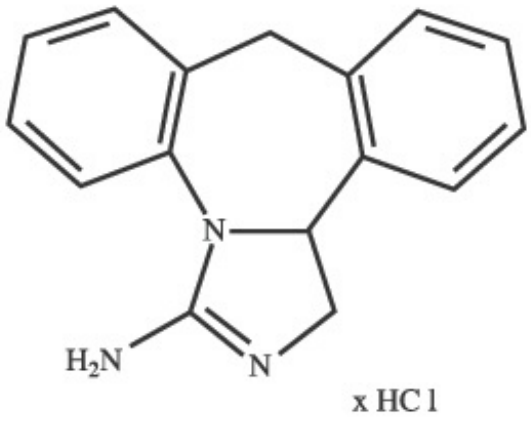
Epinastine HCl Ophthalmic Solution, 0.05%

Rx only

DESCRIPTION

Epinastine HCl ophthalmic solution, 0.05% is a clear, colorless, sterile isotonic solution containing epinastine HCl, an antihistamine and an inhibitor of histamine release from the mast cell for topical administration to the eyes.

Epinastine HCl is represented by the following structural formula:



$C_{16}H_{15}N_3 \cdot HCl$ Mol. Wt. 285.78

Chemical Name

3-Amino-9, 13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride

Each mL contains

Active: Epinastine HCl 0.05% (0.5 mg/mL) equivalent to epinastine 0.044% (0.44 mg/mL); **Preservative:** Benzalkonium chloride 0.01%; **Inactives:** Edetate disodium, dihydrate; purified water; sodium chloride; sodium phosphate monobasic, anhydrous; and sodium hydroxide and/or hydrochloric acid (to adjust the pH). Epinastine HCl ophthalmic solution, 0.05% has a pH of approximately 7 and an osmolality range of 250 to 310 mOsm/kg.

CLINICAL PHARMACOLOGY

Epinastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from the mast cell. Epinastine is selective for the histamine H_1-receptor and has affinity for the histamine H_2-receptor. Epinastine also possesses affinity for the α_1-, α_2-, and 5-HT_2-receptors. Epinastine does not penetrate the blood/brain barrier and, therefore, is not expected to induce side effects of the central nervous system.

Fourteen subjects, with allergic conjunctivitis, received one drop of epinastine HCl 0.05% in each eye twice daily for seven days. On day seven average maximum epinastine plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about two hours indicating low systemic exposure. While these

concentrations represented an increase over those seen following a single dose, the day 1 and day 7 Area Under the Curve (AUC) values were unchanged indicating that there is no increase in systemic absorption with multiple dosing. Epinastine is 64% bound to plasma proteins. The total systemic clearance is approximately 56 L/hr and the terminal plasma elimination half-life is about 12 hours. Epinastine is mainly excreted unchanged. About 55% of an intravenous dose is recovered unchanged in the urine with about 30% in feces. Less than 10% is metabolized. The renal elimination is mainly via active tubular secretion.

Clinical studies

Epinastine HCl 0.05% has been shown to be significantly superior to vehicle for improving ocular itching in patients with allergic conjunctivitis in clinical studies using two different models: (1) conjunctival antigen challenge (CAC) where patients were dosed and then received antigen instilled into the inferior conjunctival fornix; and (2) environmental field studies where patients were dosed and evaluated during allergy season in their natural habitat. Results demonstrated a rapid onset of action for epinastine HCl 0.05% within 3 to 5 minutes after conjunctival antigen challenge. Duration of effect was shown to be 8 hours, making a twice daily regimen suitable. This dosing regimen was shown to be safe and effective for up to 8 weeks, without evidence of tachyphylaxis.

INDICATIONS AND USAGE

Epinastine HCl ophthalmic solution, 0.05% is indicated for the prevention of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS

Epinastine HCl ophthalmic solution, 0.05% is contraindicated in those patients who have shown hypersensitivity to epinastine or to any of the other ingredients.

WARNINGS

Epinastine HCl ophthalmic solution, 0.05% is for topical ophthalmic use only and not for injection or oral use.

PRECAUTIONS

Information for Patients

Patients should be advised not to wear a contact lens if their eye is red. Epinastine HCl ophthalmic solution, 0.05% should not be used to treat contact lens related irritation. The preservative in epinastine HCl ophthalmic solution, 0.05%, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of epinastine HCl ophthalmic solution, 0.05% and may be reinserted after 10 minutes following its administration.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Bottle should be kept tightly closed when not in use.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In 18-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinastine was not carcinogenic at doses up to 40 mg/kg [approximately 30,000 times higher than the maximum recommended ocular human dose of 0.0014 mg/kg/day (MROHD) on a mg/kg basis, assuming 100%

absorption in humans and animals].

Epinastine in newly synthesized batches was negative for mutagenicity in the Ames/*Salmonella* assay and *in vitro* chromosome aberration assay using human lymphocytes. Positive results were seen with early batches of epinastine in two *in vitro* chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with V79 cells, respectively. Epinastine was negative in the *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinastine was also negative in the cell transformation assay using Syrian hamster embryo cells, V79/HGPRT mammalian cell point mutation assay, and *in vivo/in vitro* unscheduled DNA synthesis assay using rat primary hepatocytes.

Epinastine had no effect on fertility of male rats. Decreased fertility in female rats was observed at an oral dose up to approximately 90,000 times the MROHD.

Pregnancy

Teratogenic Effects

Pregnancy Category C

In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was approximately 150,000 times the MROHD. Total resorptions and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was approximately 55,000 times the MROHD. In both studies, no drug-induced teratogenic effects were noted.

Epinastine reduced pup body weight gain following an oral dose to pregnant rats that was approximately 90,000 times the MROHD.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, epinastine HCl ophthalmic solution, 0.05% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

A study in lactating rats revealed excretion of epinastine in the breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when epinastine HCl ophthalmic solution, 0.05% is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported ocular adverse events occurring in approximately 1 - 10% of patients were burning sensation in the eye, folliculosis, hyperemia, and pruritus.

The most frequently reported non-ocular adverse events were infection (cold symptoms and upper respiratory infections) seen in approximately 10% of patients, and headache, rhinitis, sinusitis, increased cough, and pharyngitis seen in approximately 1 - 3% of patients.

Some of these events were similar to the underlying disease being studied.

To report SUSPECTED ADVERSE REACTIONS, contact Breckenridge Pharmaceutical, Inc. at 1-800-367-3395 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in each eye twice a day.

Treatment should be continued throughout the period of exposure (i.e., until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

HOW SUPPLIED

Epinastine HCl ophthalmic solution, 0.05% is supplied sterile in opaque white LDPE plastic bottles with dropper tips and white polypropylene (PP) caps as follows:

5 mL in 10 mL bottle	NDC 51991-836-75

Storage

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed and out of the reach of children.

Distributed by:
Breckenridge Pharmaceutical, Inc.
Boca Raton, FL 33487

Manufactured by:
PrimaPharm, Inc.
San Diego, CA 92121

2323 08/13

PRINCIPAL DISPLAY PANEL - 5 mL Bottle Label

Breckenridge
Pharmaceutical, Inc.

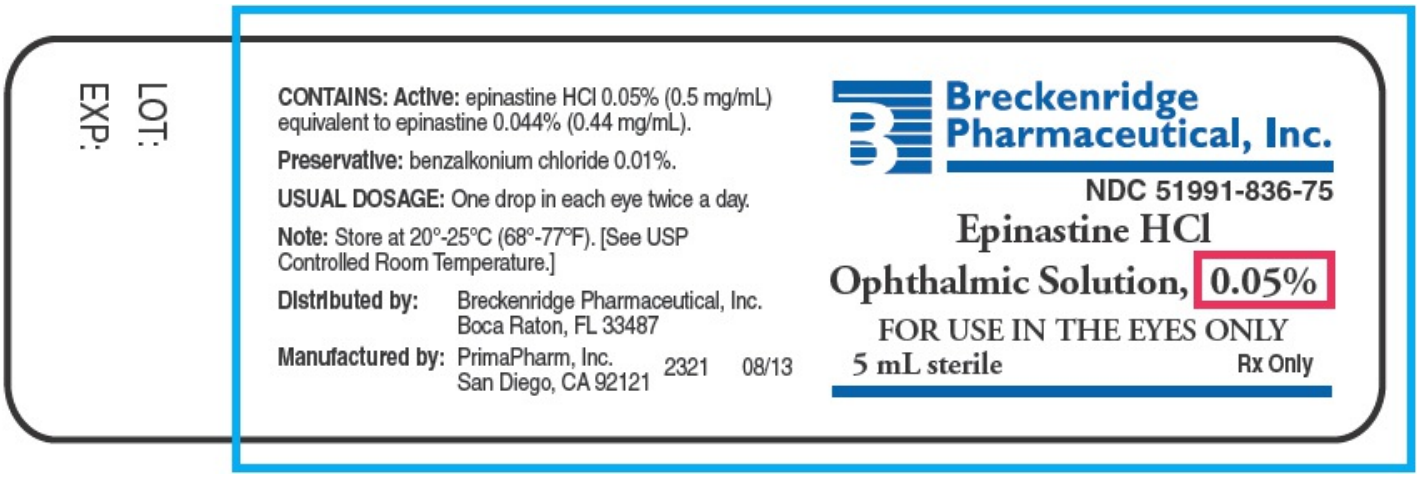
NDC 51991-836-75

Epinastine HCl
Ophthalmic Solution, 0.05%

FOR USE IN THE EYES ONLY

5 mL sterile

Rx Only



EPINASTINE HYDROCHLORIDE

epinastine hydrochloride solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51991-836
Route of Administration	OPHTHALMIC	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Epinastine Hydrochloride (UNII: GFM415S5XL) (Epinastine - UNII:Q13WX941EF)	Epinastine Hydrochloride	0.5 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
benzalkonium chloride (UNII: F5UM2KM3W7)	0.1 mg in 1 mL
edetate sodium (UNII: MP1J8420LU)	
water (UNII: 059QF0KO0R)	
sodium chloride (UNII: 451W47IQ8X)	
sodium phosphate, monobasic, anhydrous (UNII: KH7I04HPUU)	
sodium hydroxide (UNII: 55X04QC32I)	
hydrochloric acid (UNII: QTT17582CB)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:51991-836-75	1 in 1 CARTON		
1		5 mL in 1 BOTTLE, DROPPER		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA090870	11/05/2013	

Labeler - Breckenridge Pharmaceutical, Inc. (150554335)

Establishment

Name	Address	ID/FEI	Business Operations
PrimaPharm, Inc.		872805510	MANUFACTURE(51991-836)

Revised: 10/2013 Breckenridge Pharmaceutical, Inc.